

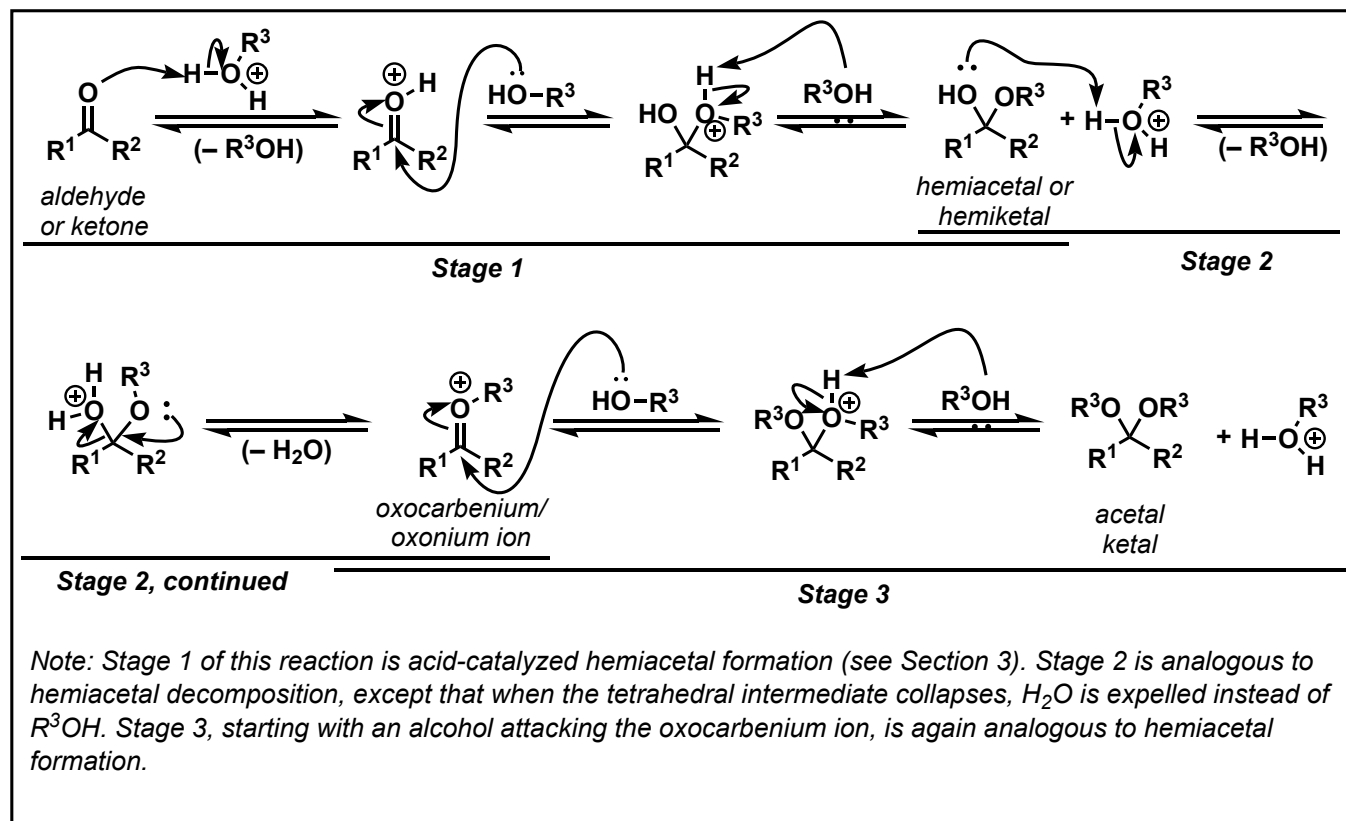
Chemistry 17: Section Handout 6

Topics: acetal formation and hydrolysis, imine and enamine formation and hydrolysis, reductive amination, Strecker amino acid synthesis

Key Concept Review

Acetal, Imine, and Enamine Formation: These reactions are all reversible. All proceed by mechanisms analogous to those for hemiacetal formation and decomposition. They are all (except for the hemiaminal formation step in imine/enamine formation) acid-catalyzed and **cannot** proceed under basic conditions. The overall transformations are all condensations (they expel H_2O); as a result, the equilibrium can be driven towards the product by removing water. (**Note:** for convenience we use the terms *acetal* and *hemiacetal* to name the products of reactions of alcohols with both aldehydes and ketones. Strictly speaking, the products with ketones are called *hemiketals* and *ketals*.)

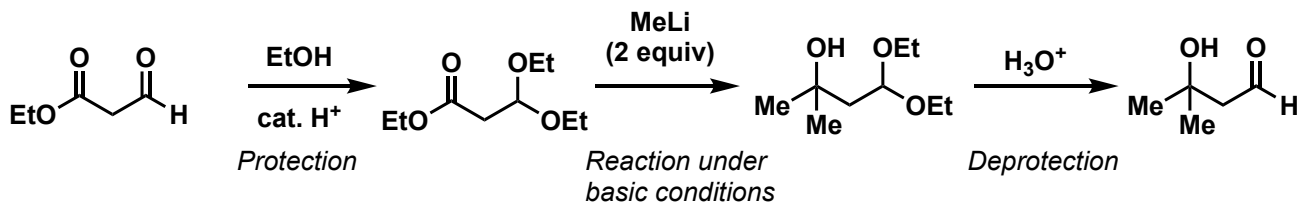
Acetal formation: An acetal is formed from the condensation of an aldehyde or ketone with two equivalents of an alcohol. The mechanism proceeds through a hemiacetal intermediate.



While hemiacetal formation can be catalyzed by acid or base, acetal formation requires acid catalysis. Hydroxide (OH^-) is not a good enough leaving group to form the requisite oxocarbenium ion intermediate until it is protonated (to leave as neutral water, H_2O). As a result, acetals are stable under basic conditions.

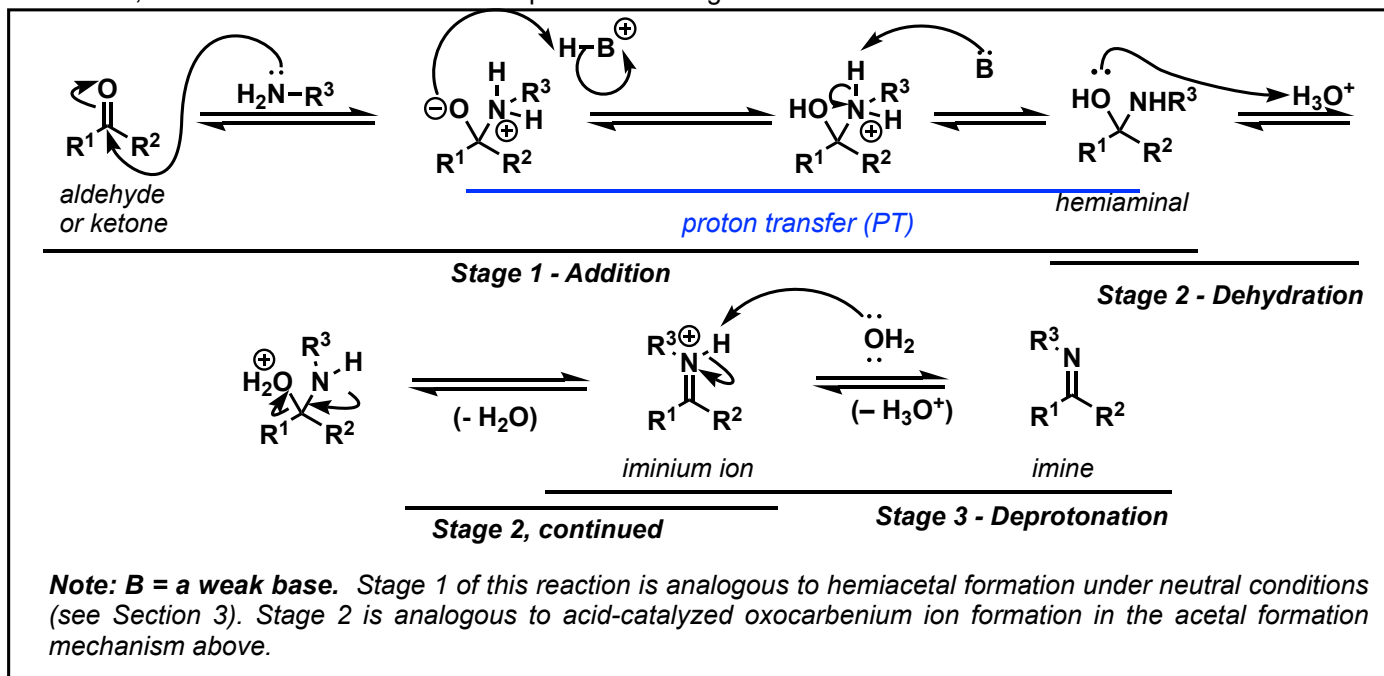
Acetals as protecting groups:

Due to their stability under basic conditions, acetals are often used as "protecting groups" to mask base-sensitive functional groups during reactions that require strongly basic reagents. After the reaction is over, the acetal protecting groups are removed with weak acid to unmask the original functional group.



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Imine formation: An imine is formed from the condensation of an aldehyde or ketone with a primary amine or ammonia; the mechanism for its formation proceeds through a hemiaminal intermediate.



Stage 1 (the "addition process") is the formation of a hemiaminal, which is analogous to hemiacetal formation under neutral conditions. Because amines are stronger nucleophiles than alcohols, they can add to the carbonyl without a catalyst. This process is actually inhibited by acid, because acid protonates the amine (thereby preventing it from acting as a nucleophile).

Stage 2 (the "dehydration process") forms the iminium ion by collapsing from the protonated hemiaminal intermediate. This stage requires an acid catalyst because hydroxide (^-OH) is a bad leaving group until it is protonated (to leave as neutral water, H_2O).

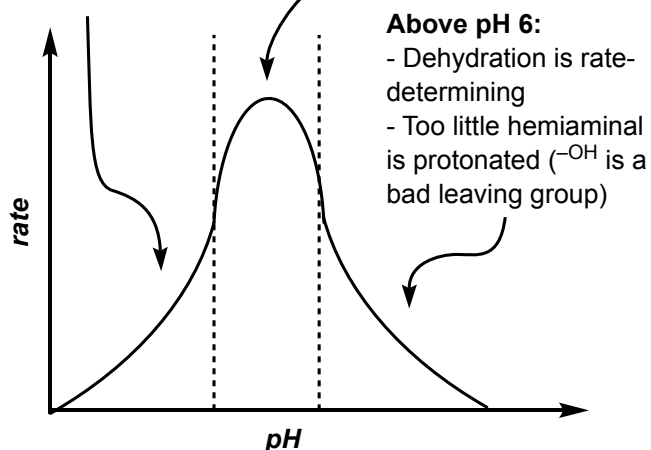
To balance the competing demands of Stages 1 and 2, **imine formation reactions are typically run at an optimal pH around 5**. Lower pH (i.e. high H_3O^+ concentration) would protonate the nucleophilic amine and inhibit Stage 1, while higher pH would prevent the acid catalysis in Stages 2-3.

Below pH 4:

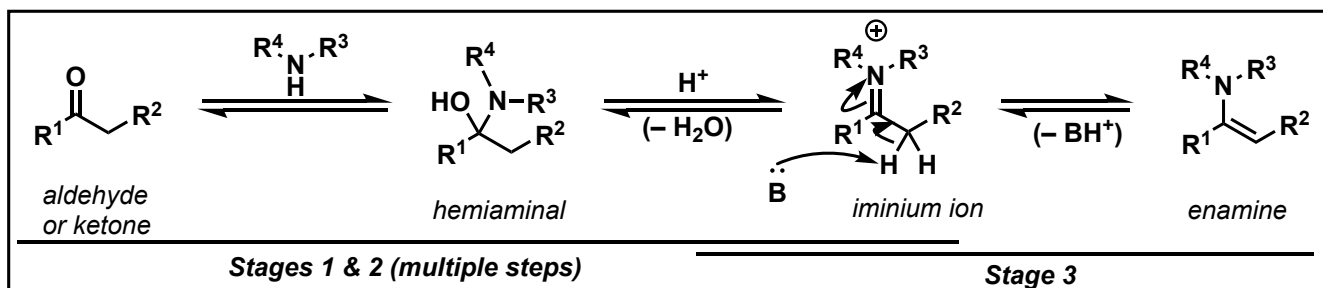
- Addition is rate-determining
- Too much amine is protonated ($R^3NH_3^+$ is a bad nucleophile)

Around pH 5:

- Addition and dehydration rates are comparable
- Hemiaminal and amine protonation are balanced



Enamine formation: An enamine is formed from the condensation of an aldehyde or ketone with a secondary amine.

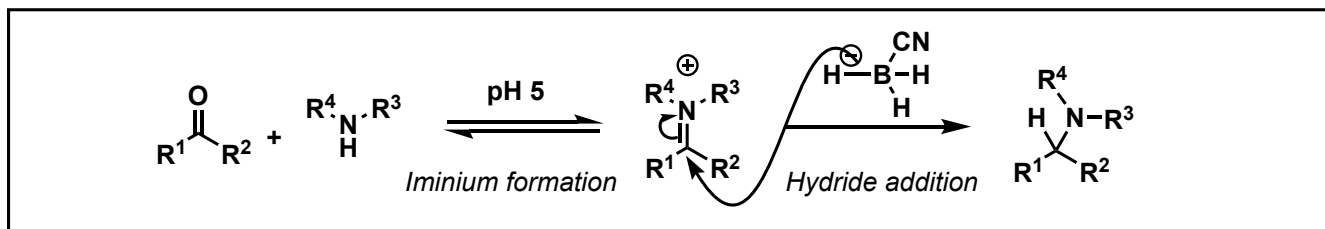


Stages 1-2 of this reaction are the same as in imine formation. At stage 3, without a proton on the cationic nitrogen, the iminium ion can be deprotonated at the remaining acidic position, the C-H alpha to the C=N bond.

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Irreversible Reactions with Iminium Ion Electrophiles: Due to the LUMO-lowering effect of positive charge, iminium ions (intermediates in the mechanisms presented above) are better electrophiles than their corresponding aldehydes or ketones.

Reductive Amination: A weak hydride nucleophile equivalent, sodium cyanoborohydride (NaBH_3CN), adds to the iminium ion electrophile to form amine products.

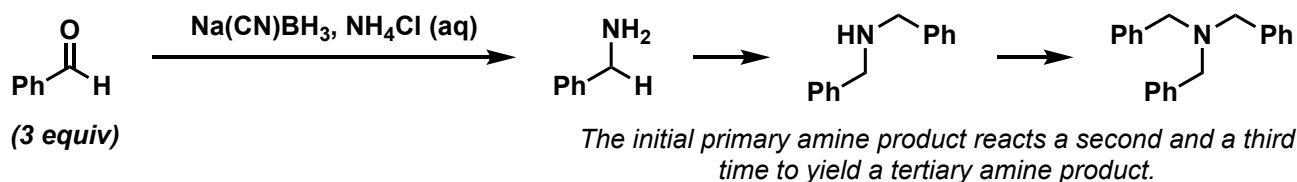


If the iminium ion is derived from a secondary amine, the product will contain a tertiary amine. If the iminium ion is derived from a primary amine, the product will contain a secondary amine. If the iminium ion is derived from ammonia, the product will contain a primary amine. When ammonia is used, *aqueous ammonium chloride* is the preferred nitrogen source because it is slightly acidic and maintains the pH around 5 (the optimal pH for iminium ion formation).

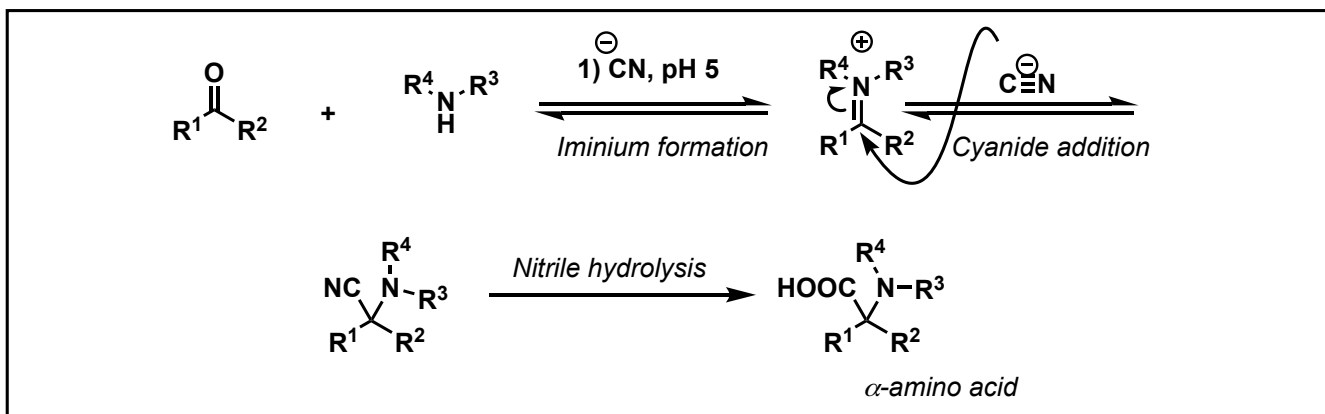
Nitrogen Source	Product
ammonia (NH_3)	1° amine
1° amine	2° amine
2° amine	3° amine

Since the starting material and products are both amines, if there is enough aldehyde/ketone and sodium cyanoborohydride the amine may react more than once.

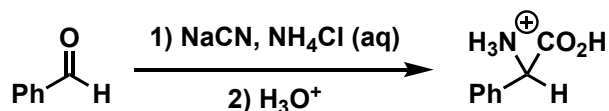
Example:



Strecker Reaction: A cyanide nucleophile adds to the iminium ion electrophile. In a separate step, the nitrile is hydrolyzed irreversibly to form α -amino acid products.



Example:

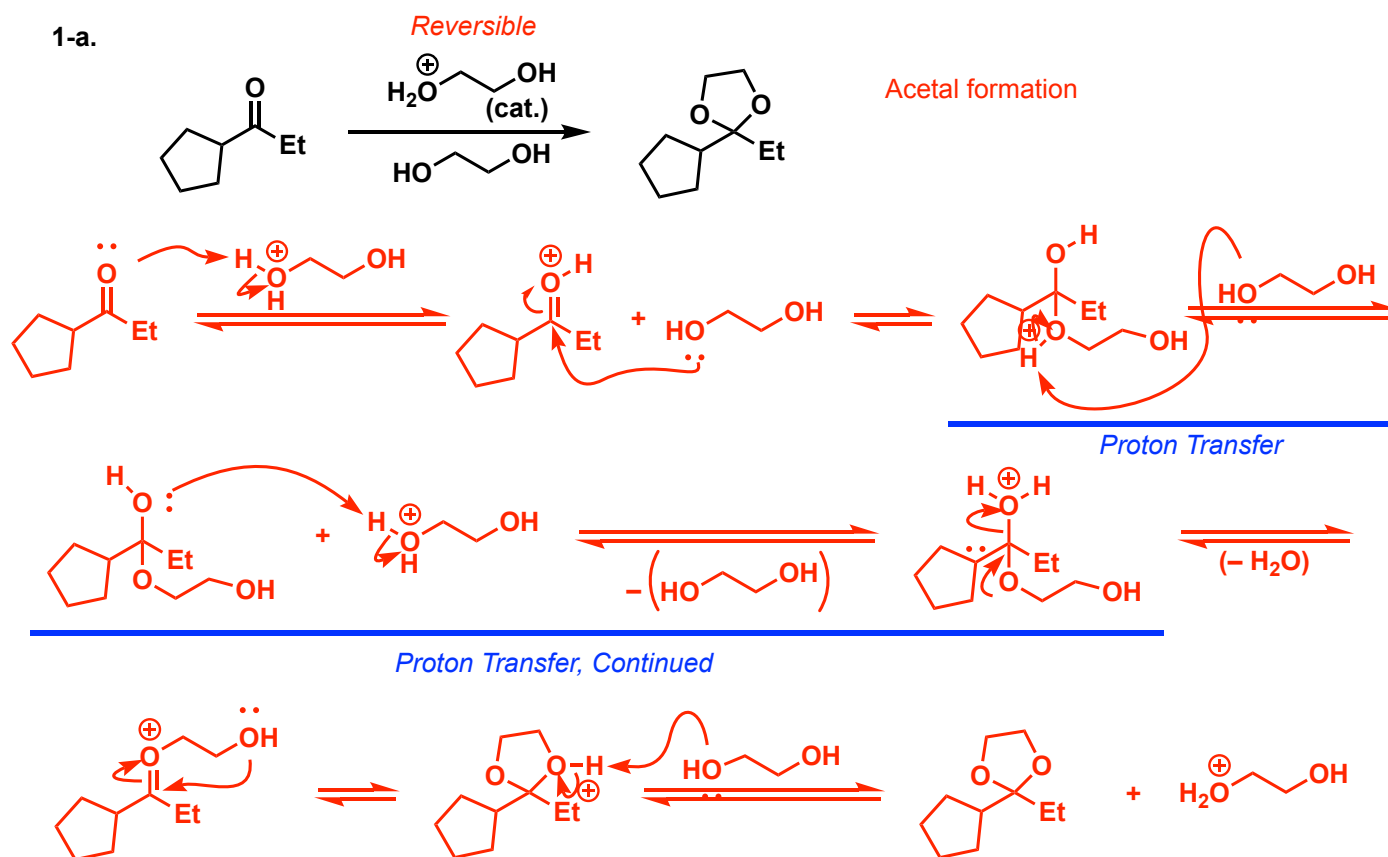


Workshop Problems

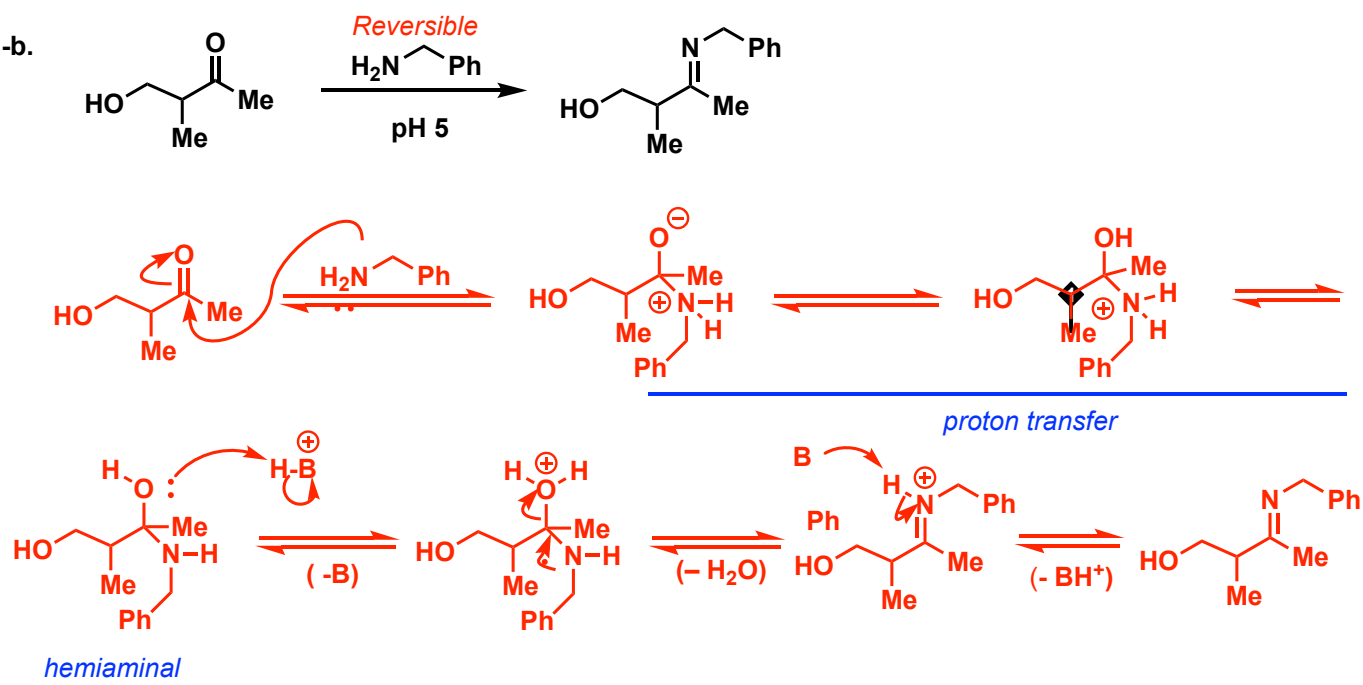
Workshop Problem 1: Mechanisms

Please propose a mechanism for each of the transformations below, using curved arrows to represent the redistribution of electrons in each step. Draw curved arrows for every step, including proton transfer steps. Indicate whether the reaction is reversible or irreversible.

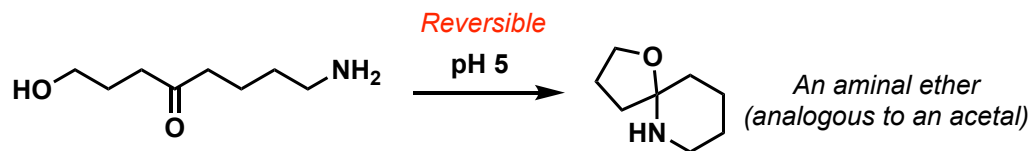
1-a.



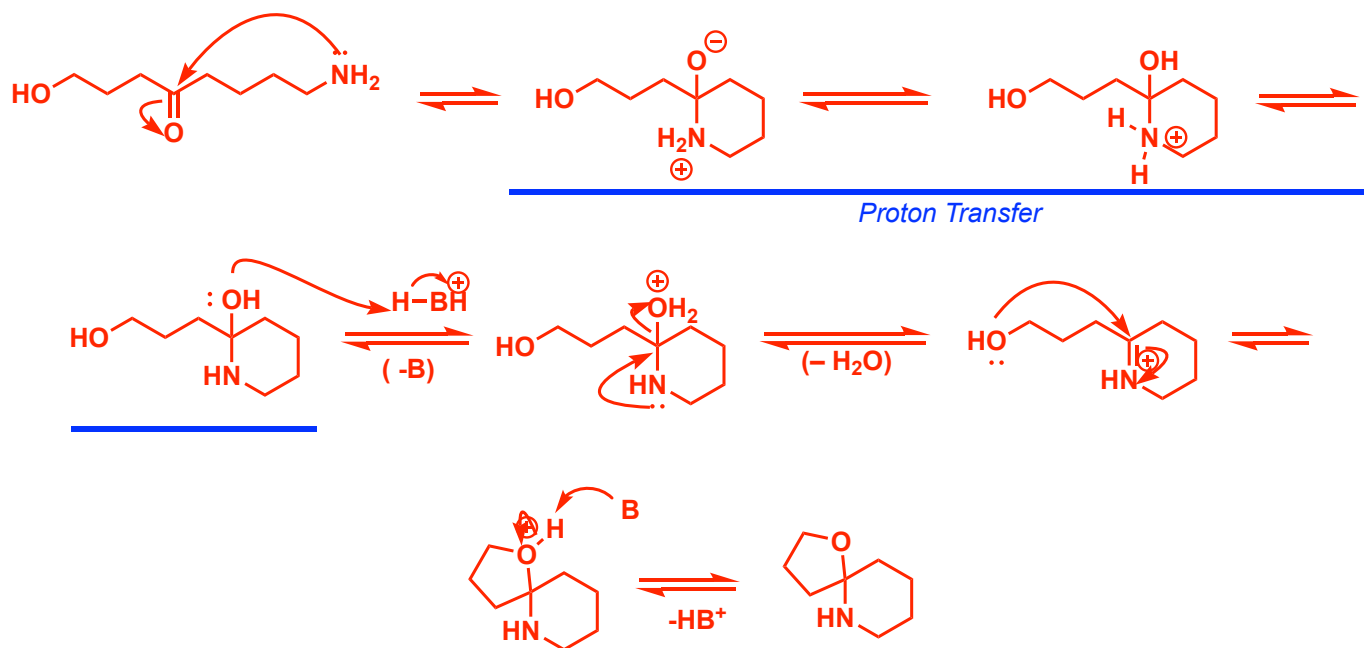
1-b.



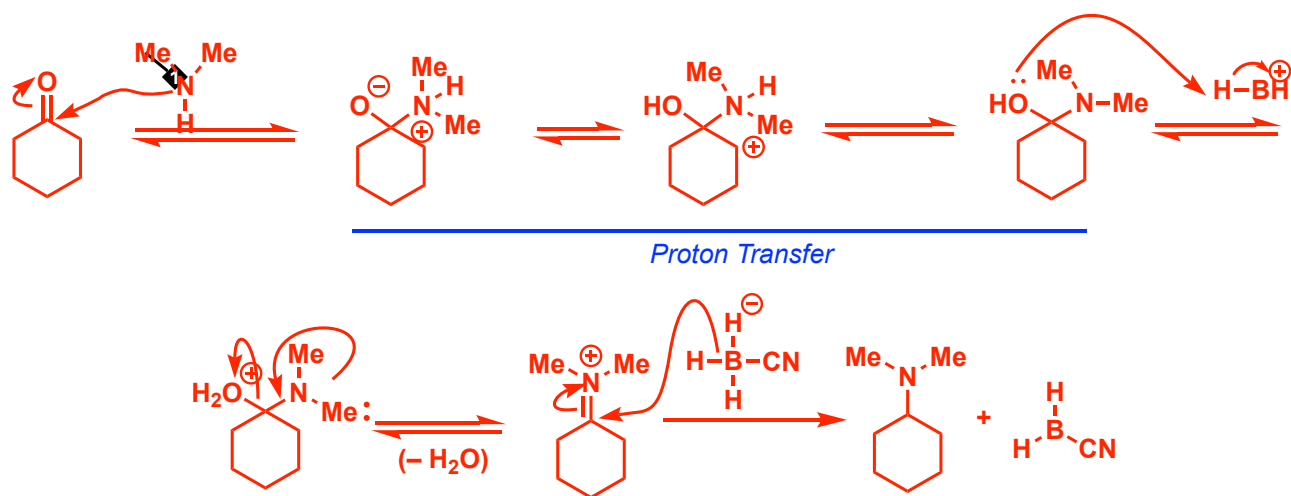
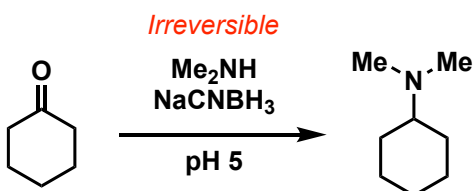
1-c.

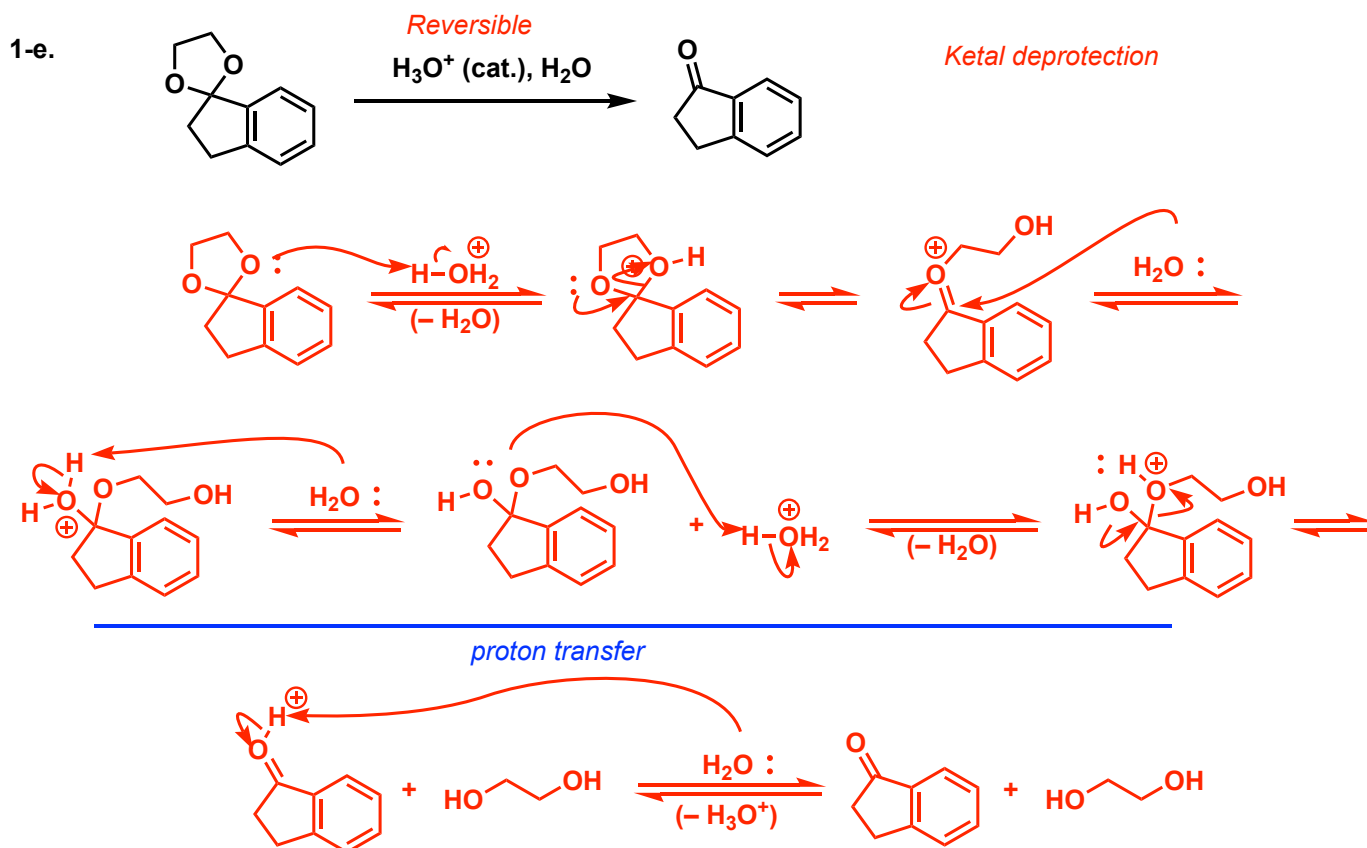


Hint: Identify the most nucleophilic site in the starting material.

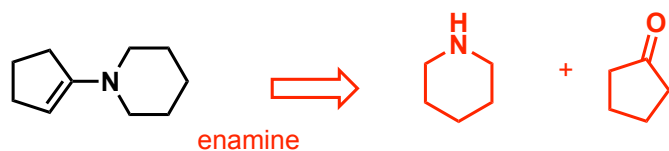
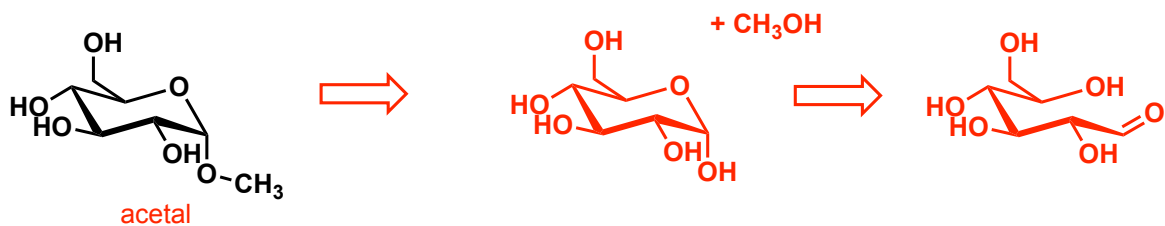
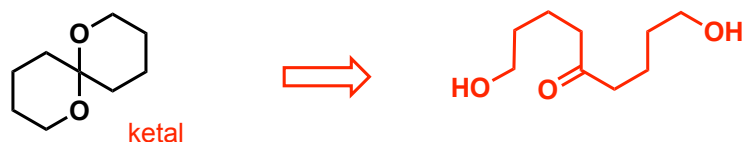


1-d.





Question 2: Label the compounds below as acetals, ketals, imines, enamines, hemiacetals/ketals or hemiaminals. Then draw the carbonyl compound and nucleophile(s) from which they are derived. Note: some of these compounds may be formed by intramolecular reactions.

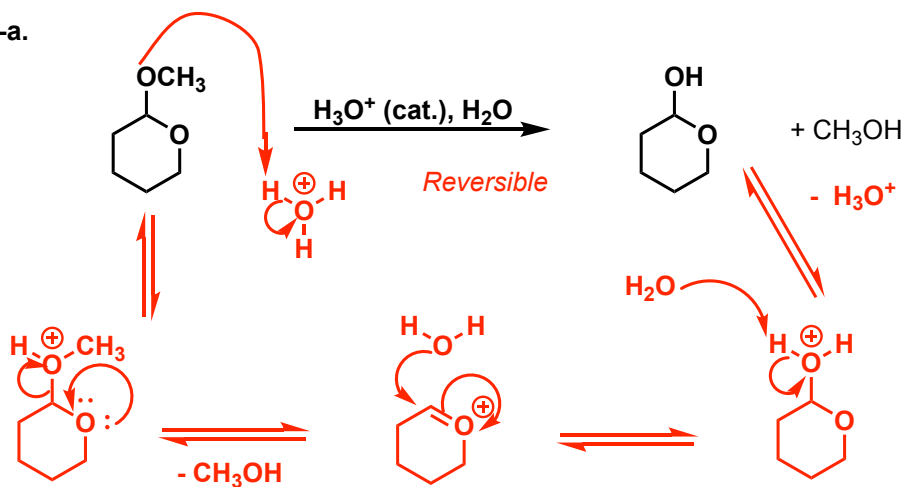


Practice Problems

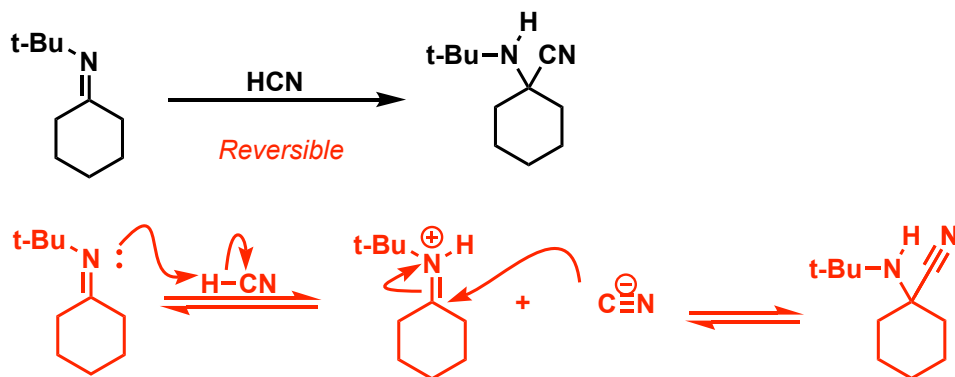
Skillbuilder Problem 1: Mechanisms (partial)

Propose a mechanism for each of the transformations below, using curved arrows to represent the redistribution of electrons in each step. Draw curved arrows for every step, including proton transfer steps. Indicate whether the reaction is reversible or irreversible.

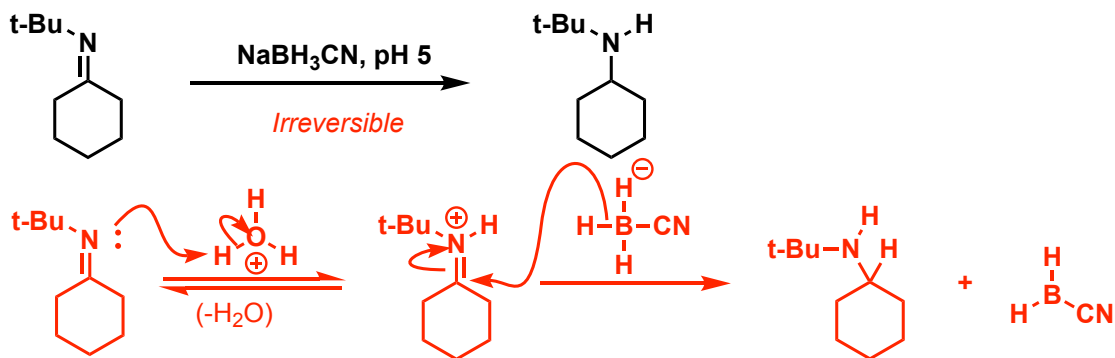
1-a.



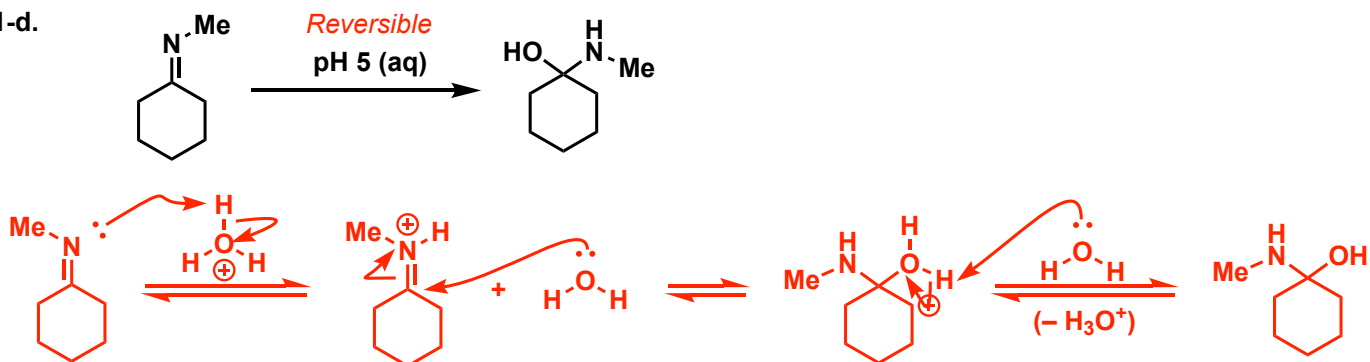
1-b.



1-c.



1-d.



Skillbuilder Problem 2: Complete Mechanisms

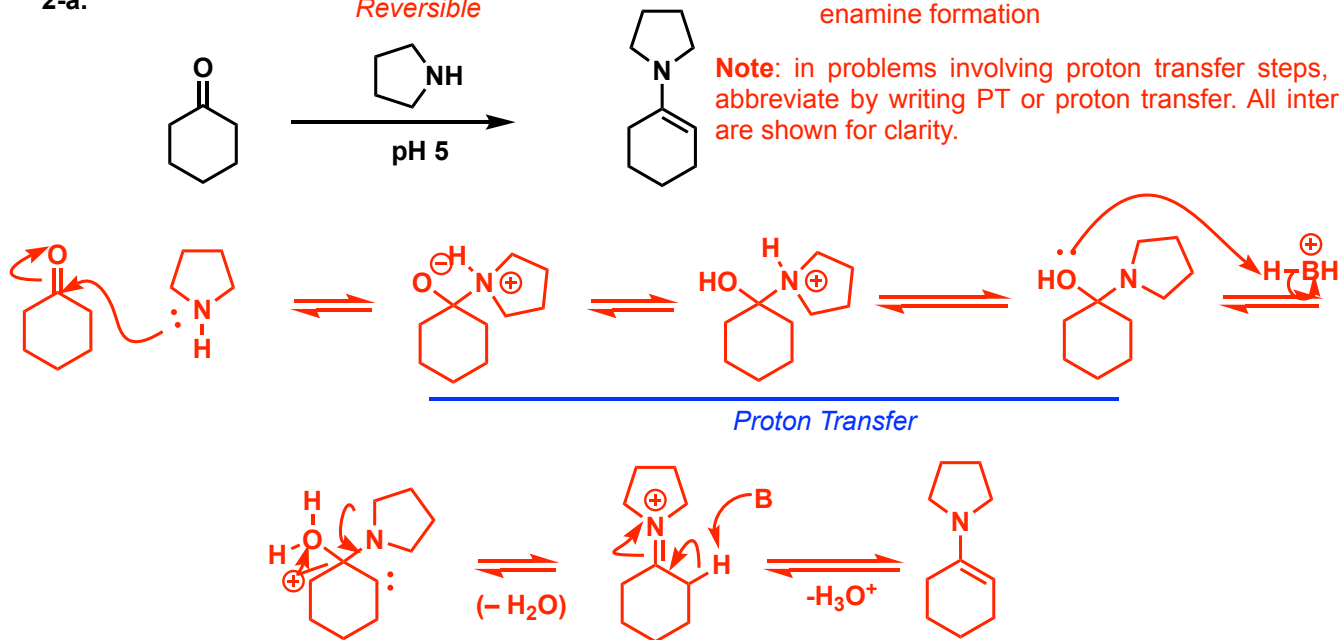
Propose a mechanism for each of the transformations below, using curved arrows to represent the redistribution of electrons in each step. Draw curved arrows for every step, including proton transfer steps. Indicate whether the reaction is reversible or irreversible.

2-a.

Reversible

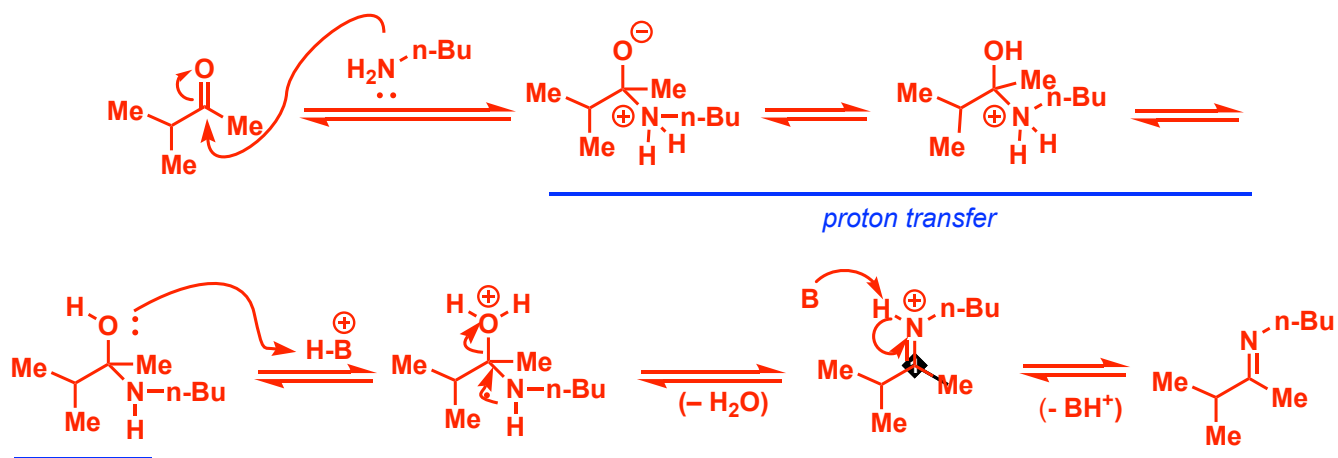
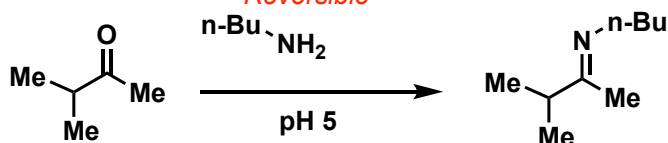
enamine formation

Note: in problems involving proton transfer steps, you may abbreviate by writing PT or proton transfer. All intermediates are shown for clarity.

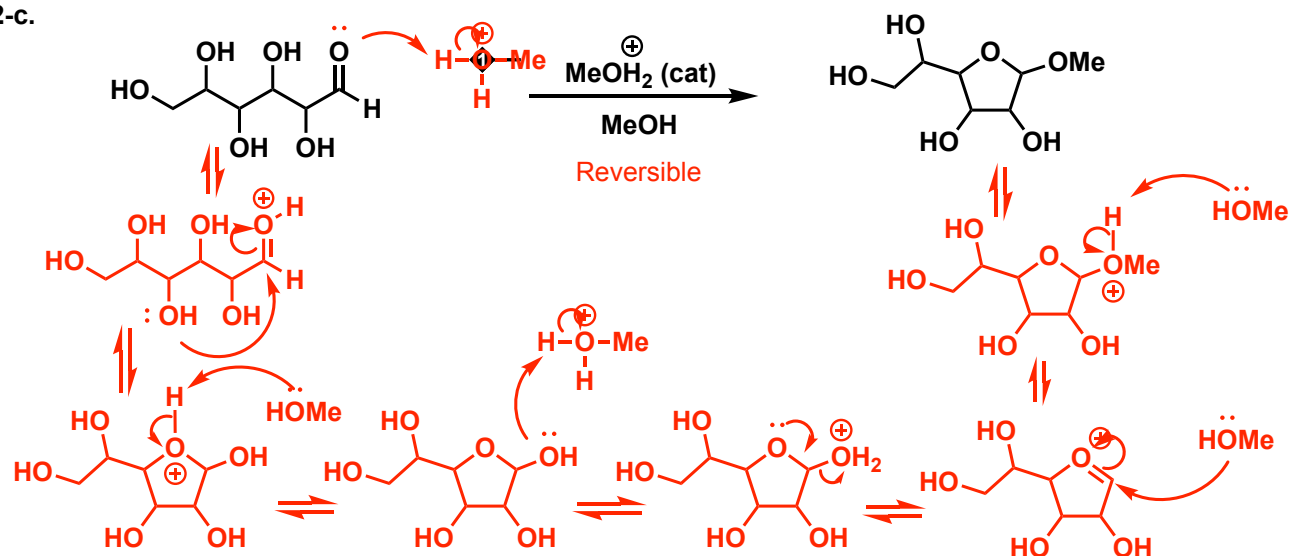


2-b.

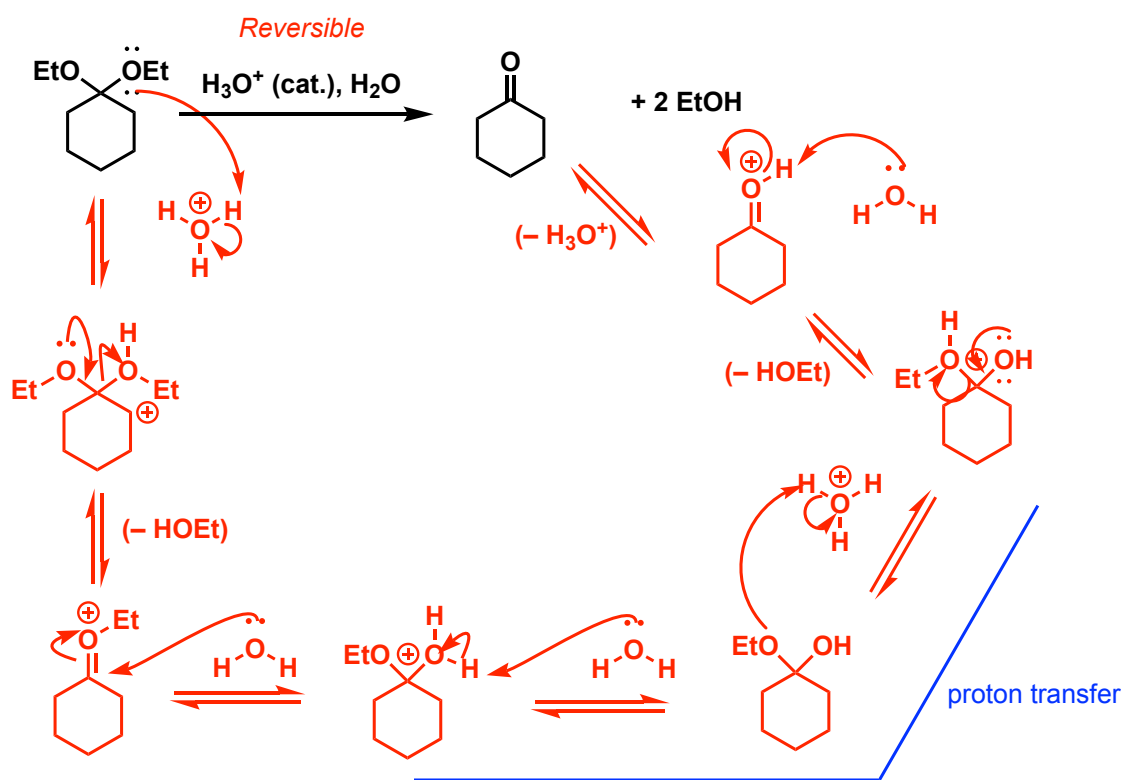
Reversible



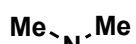
2-c.



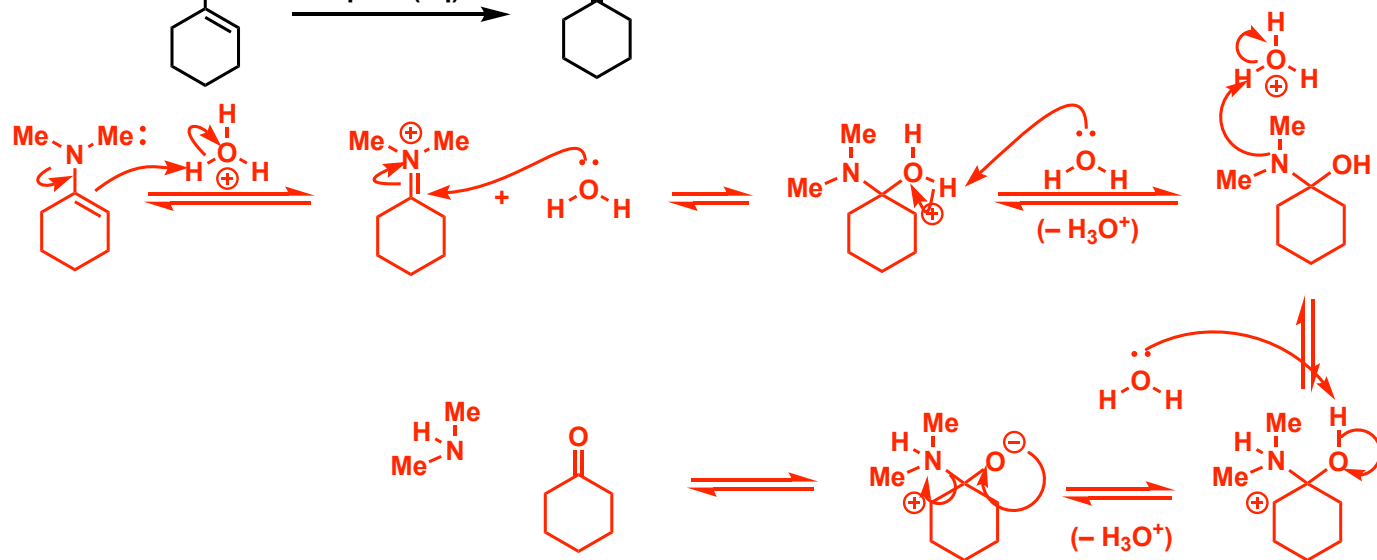
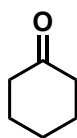
2-d.



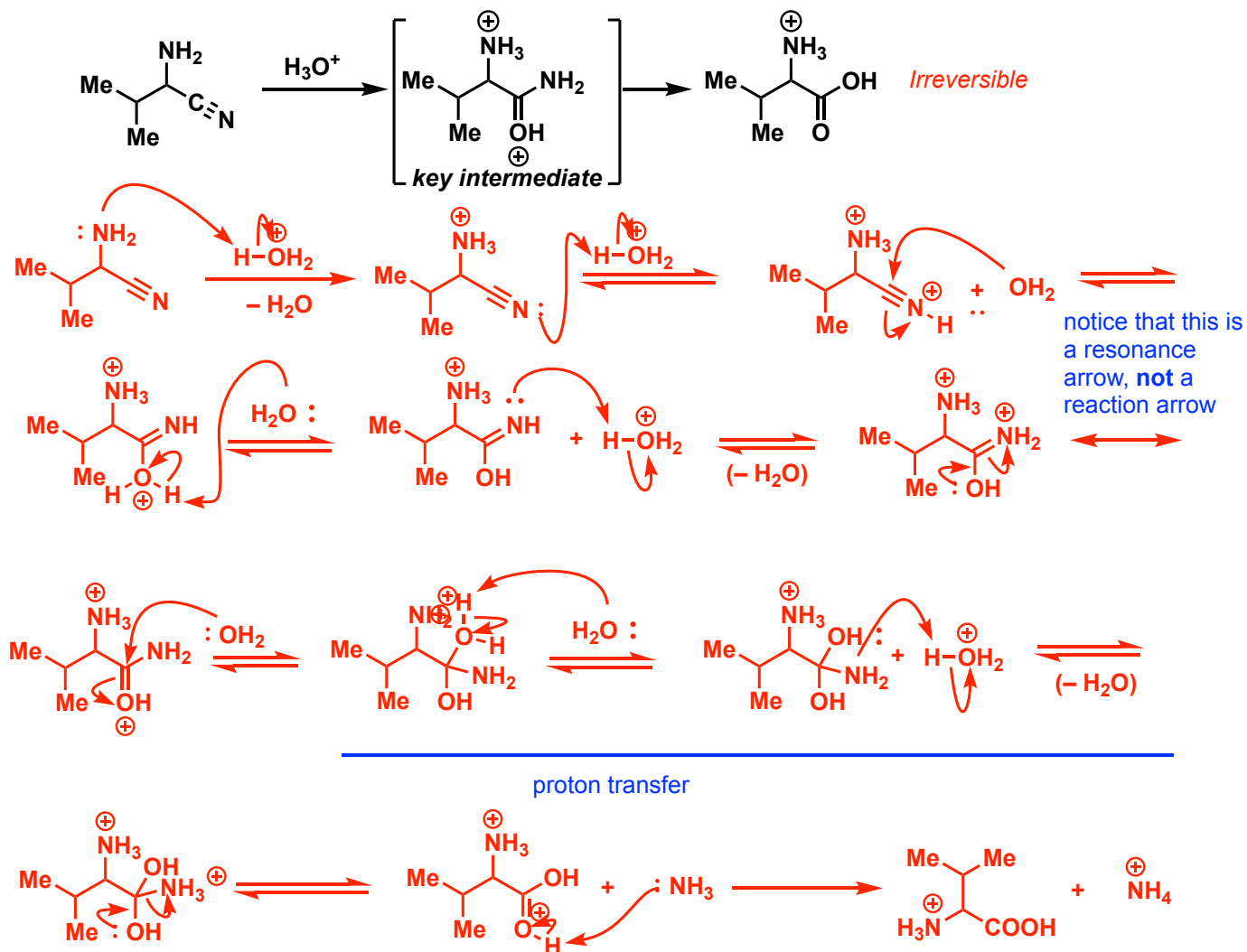
2-e.



Reversible
pH 5 (aq)

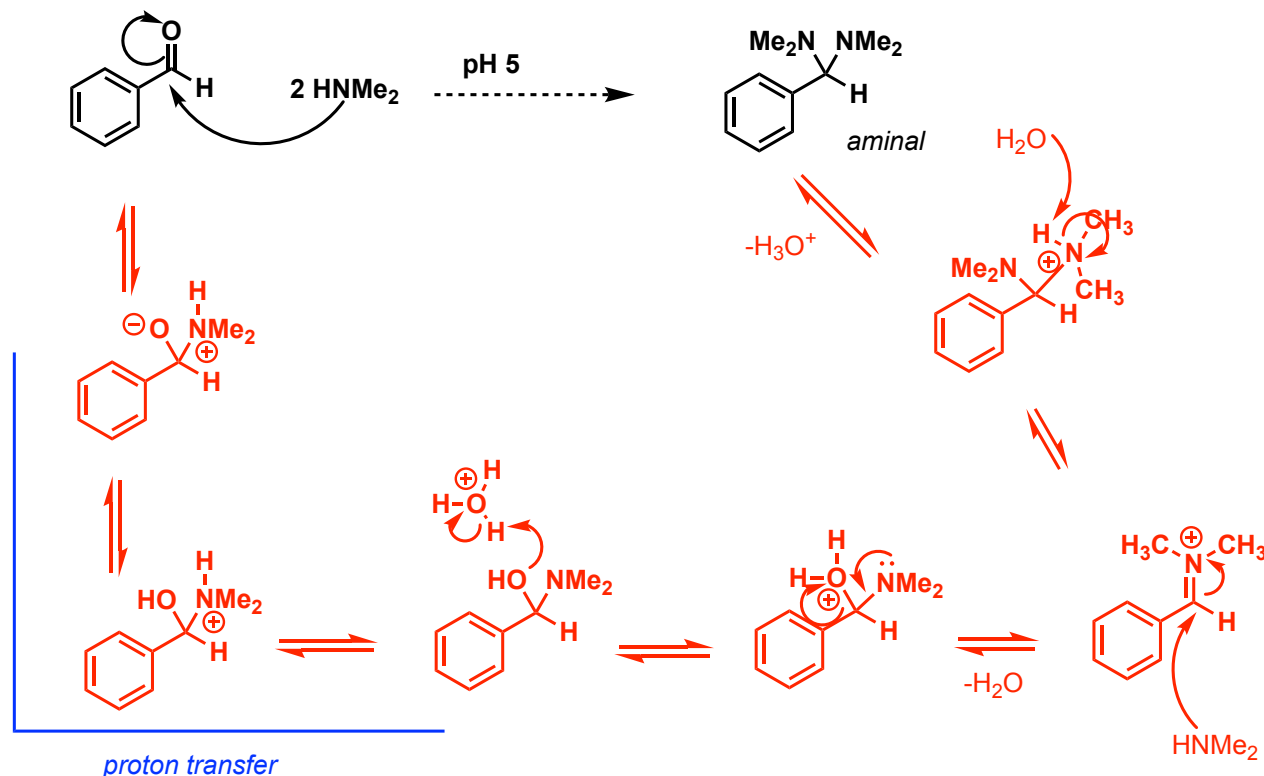


Please propose a mechanism for each of the transformations below, using curved arrows to represent the redistribution of electrons in each step. Draw curved arrows for every step, including proton transfer steps. Indicate whether the reaction is reversible or irreversible.



Challenge Problem 2:

2-a. Certain aldehydes or ketones give aminals on reaction with excess secondary amines under mildly acidic conditions. Draw the mechanism for formation of this product using curved arrows to depict the redistribution of electrons in each step. Clearly indicate whether each step is reversible or irreversible by using the correct reaction arrow.

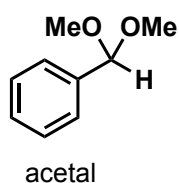
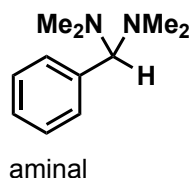


2-b. By considering the structure of the iminium ion intermediate, explain why the aminal product forms in this reaction and not an imine or an enamine.



- The intermediate iminium cannot become a neutral imine by loss of H⁺ from N, as the nucleophile was a secondary amine. The iminium ion therefore persists as a reactive electrophile in the reaction medium to be trapped by a nucleophile.
- The iminium ion also does not have an acidic α C-H that can be lost to form an enamine, and so its only pathway to form a neutral product is by attack of a nucleophile on the iminium.

2-c. Acetals are common and stable structures whereas aminals are much less common and often unstable. Propose an explanation for the difference based on the structures shown below.



There is greater steric congestion in the aminal structure due to the two R substituents on each N as compared to a single R substituent on each O. There is a greater steric penalty for forming the sp³-C of the aminal product from the sp²-C of the iminium ion, than there is for forming the sp³-C of the acetal from the sp²-oxocarbenium ion.